CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021083

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Rapamune® (Sirolimus, Rapamycin) Oral
NDA No. 50-770

Item 16: Debarment Certification

Wyeth-Ayerst hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetics Act in connection with application No. 50-770 for Rapamune® Oral.

Signed:

Justin R. Victoria
Vice President
Worldwide Regulatory Affairs

Patent/Exclusivity Information

1)	Active ingredient(s)	Sirolimus
2)	Strength(s)	1 mg per 1 ml
3)	Trade Name	Rapamune®
4)	Dosage Form (Route of Administration)	Oral liquid concentrate in bottles (60 ml and 150 ml) and foil pouches (1 ml, 2 ml, and 5 ml)
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
[redacted]		[redacted]
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be submitted prior to 5 years after the date of approval of this NDA.
9)	Applicable patent numbers and expiration date of each	U.S. Patent 5,100,899, Normal Expiration Date: June 6, 2009. U.S. Patent 5,212,155, Normal Expiration Date: May 18, 2010. U.S. Patent 5,308,847 Normal Expiration Date: May 3, 2011 U.S. Patent 5,403,833, Normal Expiration Date: April 4, 2012 U.S. Patent 5,536,729, Normal Expiration Date: September 30, 2013

PATENT INFORMATION UNDER SECTION 505(b)

The use of Rapamune® (Sirolimus, AKA, rapamycin) for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,100,899, normal expiration date June 6, 2009.

The use of Rapamune® (Sirolimus, AKA, rapamycin) in combination with Cyclosporin for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,212,155, normal expiration date May 18, 2010.

The use of Rapamune® (Sirolimus, AKA, rapamycin) in combination with Cyclosporin for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,308,847, normal expiration date May 3, 2011.

The use of Rapamune® (Sirolimus, AKA, rapamycin) in combination with a Corticosteroid for inhibiting rejection in organ or tissue transplantation is covered by U.S. Patent 5,403,833, normal expiration date April 4, 2012.

The Rapamune® oral liquid formulation is covered by U.S. Patent 5,536,729, normal expiration date September 30, 2013.

An application for extension under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. The parent company of applicant is the owner of this patent. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____
Arthur G. Seifert
Patent Attorney

EXCLUSIVITY SUMMARY FOR NDA # 21-083 SUPPL # _____

Trade Name Rapamune Generic Name Sirolimus

Applicant Name Wyeth-Ayerst HFD # 590

Approval Date If Known September 15, 1999

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /__/

b) Is it an effectiveness supplement?

YES /__/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /X/ NO /__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? 5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /__/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/ 8/27/99

Signature Date

Title: RPM

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/24/99

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21083	**Trade Name:**	RAPAMUNE (SIROLIMUS)1MG/ML ORAL SOLUTION
Supplement Number:		**Generic Name:**	SIROLIMUS
Supplement Type:		**Dosage Form:**	Solution; Oral
Regulatory Action:		**Proposed Indication:**	Prophylaxis of acute rejection in renal transplant patients

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

_X_ NeoNates (0-30 Days) _X_ Children (25 months-12 Years)
_X_ Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Required studies are ongoing

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

PPSR submitted April 30, 1999 WR to be issued - August 27, 1999

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MATTHEW BACHO

/S/

Signature

8/27/99

Date

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

December 15, 1998

NDA No. 21-083

Original NDA
Request for Priority Status

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Please find enclosed a new drug application, NDA No. 21-083 for **Rapamune® (sirolimus) Oral Solution.** Rapamune® Oral Solution is a new immunosuppressant intended for the prophylaxis of organ rejection in patients receiving renal transplants. Rapamune® is intended to be administered with cyclosporine (CsA) and corticosteroids. While sirolimus is the official USAN name, the active drug is also commonly known as rapamycin, and both names have been used in the literature.

Sirolimus is a potent immunosuppressive agent which acts via a distinct mechanism of action. Because of its unique mechanism of action, sirolimus is synergistic with CsA both *in vitro* and *in vivo* and has a side effect profile that largely differs from that of other immunosuppressive agents.

Regulatory History

The original IND (IND [redacted]) for Rapamune® (sirolimus) Oral was submitted on March 17, 1992. Development of this drug was facilitated by the highly interactive relationship between the Division of Special Pathogens and Immunologic Drug Products (and formerly the Division of Anti-Viral Drugs) and Wyeth-Ayerst. A number of meetings and telecommunications were held in which key aspects of the development program were discussed and major agreements were reached. The most significant of these interactions are summarized below:

- An End-of-Phase I meeting was held on April 18, 1994. In addition to obtaining the Division's concurrence to proceed with Phase II clinical studies, the Division agreed with the approach to study Rapamune® in combination with reduced and full doses of cyclosporine. It was also confirmed that there is no requirement to demonstrate the efficacy of Rapamune® as a single agent. Subpart E designation for Rapamune® was also confirmed.
- An End-of-Phase II meeting was held on December 15, 1995. The Division agreed with the plans for two Phase III controlled studies, Protocols 301 and 302, intended to provide the primary evidence of efficacy for the indication of prophylaxis of organ rejection in renal transplant recipients. The Division recommended a composite endpoint consisting of the incidence of acute rejection, graft loss and patient survival at six months following transplantation, and this composite endpoint was adopted as the primary endpoint for both of these protocols. The Division advised that patient and graft survival at twelve months would also be needed. The choice for the

Rapamune® doses to be evaluated (2 mg/day and 5 mg/day) as well as the choice of the comparators (azathioprine in protocol 301 and placebo in protocol 302) were also agreed upon.

- Wyeth-Ayerst submitted protocols for two year carcinogenicity studies in rats and mice along with the rationale for dose selection of these studies. On March 21, 1996, FDA confirmed the dose selection for these studies was acceptable. FDA also confirmed that the results of these studies are not required for the filing or approval of the NDA.
- There were two pre-NDA meetings. The first was held on March 31, 1998 with the Division of Special Pathogens and Immunologic Drug Products regarding the chemistry, manufacturing and controls portion of the NDA. The second pre-NDA meeting was held on June 8, 1998 and was directed at assuring the adequacy of the remaining components of the NDA. There was general agreement that the content and format of the application was acceptable. The Division commented that the unique mechanism of action and the results of the Phase III efficacy studies would provide sufficient support for a priority status. A final decision will occur after the NDA submission.

Clinical Studies

The clinical program consisted of 50 studies in which more than 2800 patients and volunteers were enrolled; and 2247 of whom received at least one dose of Rapamune®. The primary source of the efficacy and safety data are derived from two large, adequate and well controlled, randomized, double-blind Phase III studies (Protocols 301 and 302) in primary mismatched renal allograft recipients. The studies were designed to demonstrate the safety and efficacy of Rapamune® in preventing the occurrence of the first biopsy-confirmed acute rejection during the first six (6) months after transplantation while maintaining acceptable patient and graft survival at 6 and 12 months. In both studies, patients received a protocol-defined regimen of CsA and corticosteroids.

One thousand two hundred ninety-five (1295) patients were enrolled in the two studies; seven hundred nineteen (719) patients were enrolled in the azathioprine-controlled study (Protocol 301); and five hundred seventy-six (576) patients in the placebo controlled study (Protocol 302).

The results demonstrate that Rapamune® therapy (2 mg/day and 5 mg/day) in conjunction with CsA and corticosteriods was more effective than the control groups. Statistically significant improvement favoring the Rapamune® groups was noted for the composite primary endpoint, and several secondary endpoints; such as, rate of first acute rejection during the first six months; distribution of grades of rejection toward milder rejection; and reduction of the use of antibody therapy to treat the first episode of acute rejection. The benefits were achieved while maintaining a one-year patient and graft survival of > 94 % and > 91 % respectively. The safety profile which emerged from the Phase III studies was similar to what has been observed in earlier trials. Treatment with Rapamune® was associated with predictable, dose-related side effects that were: 1) reversible with dose reduction or discontinuation, and 2) associated with an acceptable incidence of discontinuation not associated with acute toxicities. These events included diarrhea, arthralgia, peripheral edema, some laboratory abnormalities such as elevated serum lipids and decreased platelet counts. There was no observed adverse effect on patient or graft survival, nor was there an increased incidence of pregnancy.

Request for Priority Status

Acute allograft rejection occurring within the first 6 months following transplantation continues to be a significant clinical problem despite recent advances in immunosuppressive drug regimens. Severe acute rejection episodes (those diagnosed within the first 6 months after transplantation), especially those of severe grade or with permanent functional deterioration, are frequently associated with a higher incidence and an earlier onset of chronic rejection and shortened graft longevity. Thus,

an immunosuppressive regimen that includes a safe drug with a novel mechanism of action, and that could demonstrate improvement in acute allograft rejection rates while maintaining or improving graft and patient survival, would represent an advancement in the field of transplantation.

Accordingly, based on: 1) Rapamune's® novel mechanism of action; 2) the design features of the Phase III studies of Rapamune® and the compelling results; 3) the grave consequences of graft rejection and limited therapeutic options in the field of transplantation, Wyeth-Ayerst requests priority status for this NDA.

NDA Content and Format

NDA No. 21-083 and **User Fee ID** [redacted] have been pre-assigned to this application. The paper copy of this application contains a total of 363 volumes, with 362 volumes numbered consecutively and one alpha-numeric volume, 100a. Included in these volumes are Items 1, 2, 3, 4, 5, 6, 8, 10, 13, 14, 16, 17, and 18. Item 11 (case report tabulations) and Item 12 (case report forms) are provided in electronic form per FDA guidance (*Archiving Submissions in Electronic Format - NDAs;* issued September 1997). The archival copy of the electronic files is provided on tape with [redacted] The files are organized in study directories; the two directories are entitled: ***CRT/DOMAINS*** (Item 11) and ***CRF***(Item 12). There is a table of contents file in each directory: ***crttoc.pdf*** and ***crftoc.pdf***, respectively. Indexes entitled: ***crt.pdf*** and ***crf.pdx,*** respectively, have been prepared for each directory and appear in the ***INDEXES*** directory. Please note that the submission files have been tested with McAfee VirusScan (version 3.0.2) and no viruses were discovered. The archival electronic submission of Item 11 and Item 12, as compiled, is 2.9 gigabytes and is provided on one tape in a separate binder accompanying the paper submission.

An electronic regulatory review aid will be provided using a Wyeth-Ayerst server located at the FDA Corporate Boulevard facility, Gaithersburg, MD; currently, it is planned for installation on December 18, 1998. In this electronic review aid, the NDA paper volumes will be provided as PDF files with a detailed overall table of contents containing hyperlinks and bookmarks that will open the appropriate volume. For ease of review, a copy of the archival files for Item 11 and Item 12 will be included in the electronic regulatory review aid. Additionally, SAS datasets of clinical data, OEB datasets of the nonclinical carcinogenicity studies, and ASCII datasets for the clinical pharmacology/pharmacokinetic studies will be provided as part of the review aid.

In closing, if there are any questions concerning this application, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

rbb/rapamune/NDA 21-083.doc

cc: Ms. Mary Dempsey

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

December 22, 1998

NDA No. 21-083

Ms. Mary Dempsey
Project Manager
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
9201 Corporate Blvd.
Rockville, MD 20857

Dear Ms. Dempsey:

Reference is made to our NDA No. 21-083 for Rapamune® (Sirolimus) previously submitted to the Division of Special Pathogens and Immunologic Drug Products.

Reference is also made to your December 21, 1998 request for, additional "Desk Copies" of Volume 1 of the NDA, and an electronic version of the package insert. The purpose of this submission is to provide the requested items.

Accordingly, enclosed you will find:

1. Two (2) copies of Volume 1 of the NDA.
2. An electronic Microsoft Word version of the package insert on a 3.5" diskette.

   This diskette contains two files:

   - Package Insert.doc - A file containing the Package Insert exactly as presented in the NDA.
   - Patient Labeling.doc - A file containing the text portion of the Patient Labeling exactly as it is presented in the NDA.

For your protection, the diskette has been scanned for viruses and none were detected.

If you have any questions regarding this submission, please contact me at (610) 902-3798

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

NEW CORRESP

ORIGINAL

WYETH-AYERST RESEARCH

NC

'OX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

January 6, 1999

NDA No. 21-083

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (Sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to the January 4, 1998 telephone communication between myself and Ms. Mary Dempsey, Project Manager of your staff. In the above-referenced communication, it was explained that due to an inadvertent error in the final phases of publishing the NDA, the portion of the text in the nonclinical pharmacology and toxicology section of the Application Summary (Volume 2; Item 3.5) was omitted. The purpose of this submission is to provide an updated Volume 2 which contains the missing text and is intended to replace the previously submitted volume in its entirety.

Additionally, due to the changes in the pagination of Volume 2, we have revised the NDA Table of Contents contained in Volume 1. As such we are also providing a replacement Volume 1 in its entirety. No other changes have been made to this volume.

Accordingly, this submission contains: 1 review copy and 1 archival copy each of the revised Volumes 1 and 2. As we had provided 7 desk copies of these volumes at the time of our original NDA submission, we are also providing the same number of corresponding replacement desk copies.

Furthermore, changes will need to be made to the Electronic Regulatory Submission (ERS) in order for it to be consistent with the paper copy. Wyeth-Ayerst will contact the appropriate Information Technology person at FDA in order to arrange a time to update the FDA server. Arrangements will need to be made to update the two (2) laptops which were provided.

We apologize for any inconvenience this may have caused in the review of this application. If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen O'Skowronek

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

cc. Ms. Mary Dempsey

rbb/243.doc

DUPLICATE

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX:

Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIG AMENDMENT

January 14, 1999
Response to FDA for Information

NDA No. 21-083

BM

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA 21-083 for Rapamune® (Sirolimus) Oral Solution.

In response to the requests made by Dr. Tony Carreras, of the Division of Scientific Investigations, and Dr. Marc Cavaille-Coll, of your staff, we are providing site specific information relative to Studies 301 and 302. The information is as follows:

- ATTACHMENT 1. A list of the investigators, study sites, and the number of patients enrolled at the respective sites for each study. A specific 5 digit investigator number is presented in parentheses directly after the investigator's name. Note that the first three numbers reflect the study number (i.e., 301 or 302); the last two numbers are specific to the investigator. These specific 5 digit numbers are used in the subsequent tables and listings.

- ATTACHMENT 2. A listing of the serious adverse events by study site for each study. We have defined serious adverse events as: death; patients with graft loss; malignancies; or life-threatening adverse events.

- ATTACHMENT 3. The number of discontinuations per site observed for each study. This is the total number of discontinuations observed at the respective sites regardless of the treatment group assignment.

- ATTACHMENT 4. A listing of the reasons for discontinuations observed for each study. This listing presents the information by investigator and by treatment group.

For each investigator, information relative to the 2 mg sirolimus group is presented first, followed by the 5 mg sirolimus group, and finally followed by the respective control group.

- ATTACHMENT 5. A tabular presentation of clinical site information for studies 301 and 302. For each study the data are presented by investigator and by treatment group. The parameters are: number of patients enrolled; number of patients at the primary efficacy endpoint; number of discontinuations; and the number of serious adverse events. Please recall that the primary endpoint is defined as efficacy failure at six months; i.e., the composite of the first occurrence of acute rejection, death, or patient with graft loss. Serious adverse events are defined as deaths, graft loss, malignancies, and life-threatening events.

This information was forwarded to the Division in a series of facsimiles dated January 12, 13, and 14.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

MDS/mts/114

cc: Ms. Mary Dempsey, FDA, CDER, Division of Special Pathogens and Immunologic Drug Products (cover letter)
Dr. Tony Carreras, Office of Compliance (DSI) (w/attachments)

WYETH-AYERST RESEARCH

P.O. BOX 8299, PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

U.S. REGULATORY AFFAIRS

February 23, 1999

Rapamune® Oral Solution
NDA No. 21-083

Request for Expedited Review

Mr. Matt Bacho
Division of Special Pathogens & Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation & Research (HFD-590)
ATTN: Document Control Room
9201 Corporate Blvd.
Rockville, MD 20850

Dear Mr. Bacho:

Attached for your review are revised labels for Rapamune® Oral Solution, 1mL, 2mL, and 5mL foil pouch presentations. In this revised version we have enlarged the line "Oral Solution 1 mg/mL," as requested by Dr. M. Seggel, to be the same size as the established name, sirolimus. Additionally, we have moved the NDC number to the right to accommodate the aforementioned change. We are providing the revised label in color at actual size and 2x actual size, as requested. At this time we would like confirmation that the labels are considered acceptable. We also request an expedited review of the labels.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

mds/mts/bacho

4-1380

WYETH-AYERST RESEARCH ORIGINAL

NEW CORRESP

NC

BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3510
FAX (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

March 11, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

On March 11, 1999 we received a question from Dr. R. Tiernan, of your staff, regarding her review of the NDA. In her review, she noted that the case report tabulations (or DPRs) for the sample of renal biopsy results from the local pathologist and the central pathologist were provided for Protocol 302. She requested that these DPRs be provided for Protocol 301.

The purpose of this submission is to provide the requested files. These files are being provided in electronic PDF format and are contained on a single diskette. The ERS which is housed on a server at FDA will be updated to include these files in the future.

Accordingly, enclosed please find a single diskette containing the following files for Protocol 301:

- Renbiop2.pdf - DPR for renal biopsy results for the local pathologist.
- Renbiopa.pdf - DPR for renal biopsy results for the central pathologist.

Rapamune® (Sirolimus)
NDA No. 21-083

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho with 1 desk copy

rbb/288.doc

WYETH-AYERST RESEARCH

ORIGINAL

BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIG AMENDMENT
SU

March 15, 1999

NDA No. 21-083

3 Month Safety Update Report

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

The purpose of this submission is to provide the 3 Month Safety Update Report for the above referenced new drug application. The time frame for this submission was agreed to by the Division at our June 8, 1998 Pre-NDA meeting.

The content and format of this report was the subject of our written communication dated September 29, 1998 (Serial No. 351) which was filed to IND [redacted] On October 30, 1998, we received the Divisions concurrence that the plans for this report were acceptable. We also obtained the Division's concurrence to provide the written summary in paper and corrected case report tabulations (also known as DPRs) and updated case report forms (CRFs) electronically as per the Division's March 2, 1999 facsimile.

Please be advised that in response the Division's request to obtain information on all patients relative to the 12 month patient and graft survival, updated analyses of 12 month patient and graft survival are included in this report. These updated analyses include the majority of the patients who were noted as "lost to follow-up" in our original NDA. Under separate cover, we intend to provide detailed information regarding these patients. Our efforts to obtain this information for all patients is ongoing. We will update the NDA regarding our efforts for the remaining outstanding data. The information relative to 12 month patient and graft survival can be found in Sections 2.1.6.8.1.2.2 and 2.1.6.8.1.2.3 of this report.

Furthermore, this report contains an analysis of the incidence of acute rejection in the first 12 months of therapy for the two Phase III safety and efficacy trials (Protocols 301 and 302). We are in the process of analyzing these data for months 7-12 in accordance with the comment contained in the Division's March 2 facsimile and we will provide this is the near future along with a complete response to all items in that facsimile.

With regard to the aforementioned DPRs, we noted during the preparation of the safety update that six (6) DPRs relative to laboratory and vital sign data pertaining to the Phase III studies (Group 1) were provided incorrectly in the original NDA. These reports as listed in the integrated summary of safety were supposed to be analyzed by donor source, and were titled that way in the original NDA. However, due to a inadvertent programming error, the analysis was not done by donor source. The error has since been corrected and we have included the updated DPRs, analyzed by donor source, as part of this submission.

This submission is organized as follows:

1. Item 9: 3 Month Safety Report Summary (paper).
2. Item 11: Corrected Case Report Tabulations/DPRs (electronic PDF format).
3. Item 12: CRFs associated with the safety update (electronic PDF format).

Please note that the electronic files of this submission are being provided as the archival copy to the Central Document Room.

If you have any questions regarding this submission, please contact me at (610) 902-9898.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

Mr. Matt Bacho with 3 desk copies

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

BM

March 17, 1999

NDA No. 21-083

Response to FDA Request

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

Reference is also made to our February 9, 1999 telecommunication and February 17, 1999 teleconference in which we discussed the 14 patients identified as lost to follow-up from the pivotal studies, Protocols 301 and 302. Prior to the teleconference, a list of the individuals by site with the corresponding reasons for the loss in these patients was forwarded to the Division by facsimile. Dr. Cavaille-Coll, Medical Team Leader, requested that patient and graft survival data be obtained for these patients.

In order to provide survival data on the lost patients, Wyeth-Ayerst contacted the study sites and asked them to extend all efforts to locate this information. In total, there were fourteen patients who had missing one-year patient (13) or graft (10) survival data.

The sites were able to determine information on 10 of the 13 patients whom patient survival data was missing. All were alive at one year. The sites were also able to locate information on 7 of the 10 patients for whom graft survival data was missing. All grafts were functioning at one year.

A re-analysis of the one year patient and graft survival data was performed based upon the updated information. These analyses were included in the 3-month safety update which was submitted on March 15, 1999, and are also attached.

ORIGINAL

The following describes the status of the four patients for whom information is still outstanding:

- The patient at Dr. Taylor's site is still alive, according to a relative, but his graft status is unknown. We are awaiting further documentation about this case.
- Two patients are from Dr. Woodle's site. Both had withdrawn consent after 189 and 33 days. The first patient was known to have lost the graft. The study personnel have requested permission from their IRB to contact these patients and are awaiting a response.
- The last patient is from Dr. Adam's site. The patient is known to be alive, but the site has been unsuccessful at contacting him to determine graft status.

Accordingly, attached please find:

- A table listing the 14 lost patients by protocol and treatment.
- An updated analysis of graft survival at 12 months.
- An updated analysis of patient survival at 12 months.

In the near future, we intend to update the Division with additional information realtive to the remaining patients.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

cc. Mr. Matt Bacho

rbb.290.doc

ORIGINAL

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX: (610) 964-5973

Division of American Home Products Corporation

VICE PRESIDENT, REGULATORY AFFAIRS

March 22, 1999

NDA No. 21-083

Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP
NC

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution, previously submitted to your Administration on December 15, 1998.

The purpose of this correspondence is to officially submit a letter authorizing FDA to refer to DMF [redacted] on behalf of this NDA. This DMF authorization letter replaces the original authorization letter contained in our NDA. As stated in the attached letter from our supplier, [redacted] the original DMF for [redacted] was replaced with a [redacted] for the sake of expediting your review of the NDA, these letters were previously sent by facsimile to the Division on March 9, 1999.

If you have any questions regarding this submission, please contact me at (610) 902-3798.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek

Maureen D, Skowronek, Director
U.S. Regulatory Affairs

cc. Ms. Deborah Pagano
Program Coordinator for Field Copy Submissions

rbb/293.doc

WYETH-AYERST RESEARCH

BOX 8299 • PHILADELPHIA, PA 19101-8299 • (610) 902-3710
FAX (610) 964-5973

Division of American Home Products Corporation

REGULATORY AFFAIRS

ORIGINAL

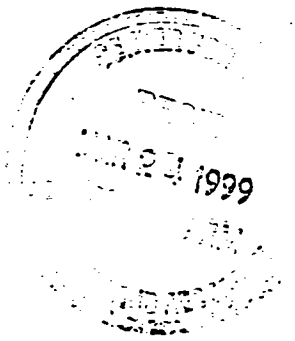
March 23, 1999

NDA ORIG AMENDMENT

BC

NDA No. 21-083

Amendment to Chemistry, Manufacturing and Controls



Mark Goldberger, M.D., Director
Division of Special Pathogens and Immunologic Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-590)
ATTN: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Goldberger:

Reference is made to our NDA No. 21-083 for Rapamune® (sirolimus) Oral Solution.

The purpose of this communication is to amend the chemistry, manufacturing and controls portion of the NDA relating to the test method for the excipient, [redacted]. In our original NDA, an [redacted] method, [redacted], was identified and provided. [redacted] which was also cited on the certificates of analysis for [redacted] is a standard [redacted] method which evaluates the samples in a closed cell. The NDA and certificates of analysis should have identified [redacted] which uses [redacted] for the evaluation of [redacted] such as [redacted] Please be advised that the [redacted] cited in the NDA, was not used for any NDA batch of [redacted] where an [redacted] identity was required. In such instances, all of the NDA batches of [redacted] were evaluated using the [redacted] identity [redacted] This inadvertent transcription error occurred in the preparation of the NDA.

Accordingly, this submission contains:

1. Revised NDA section 4.1.4.3.1 Analytical Specifications for Inactive Components. The corrected NDA specification page for [redacted] s provided.

2. A copy of analytical [redacted]

We request that this information be incorporated into the above referenced NDA.

Sincerely,

WYETH-AYERST LABORATORIES

Maureen D. Skowronek, Director
U.S. Regulatory Affairs

cc: Mr. Matt Bacho w/ 2 copies
Ms. Deborah Pagano, Program Coordinator for Field Copy Submissions